

Safety and Effectiveness of Insulin Lispro Mix 25/75 Among Filipino Patients with Type 1 or Type 2 Diabetes Mellitus: A Post-Marketing Surveillance Study

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Abstract

Background: Diabetes mellitus (DM) is a major cause of morbidity and mortality in the Philippines. Improvement in hemoglobin A1c (HbA1c) remains below recommended targets for Filipino patients. Safe and effective therapies are needed for this population.

Objective: To investigate treatment-emergent adverse events (TEAEs) and change in HbA1c among Filipino patients with DM treated with insulin lispro mix 25/75 in a real-world setting.

Materials and Methods: This was a prospective, non-interventional, post-marketing surveillance study among 459 Filipinos aged 18 years or older with type 1 or 2 DM. Patients were treated with insulin lispro mix 25/75 according to the approved label, as prescribed by the investigators, and observed for 12 weeks. Occurrence of all TEAEs and change in HbA1c from baseline to final visit were reported.

Results: Mean (SD) treatment duration was 12.93 (5.7) weeks, and mean total daily dose was 0.62 (0.29) units/kg. Eighteen patients (3.9%) experienced 23 TEAEs, the majority of which were mild. None were reported to be related to treatment. No serious TEAEs or hypoglycemic episodes were reported. Mean (95% confidence interval) HbA1c was significantly reduced by -2.03% (-2.19%, -1.87%), and 36.3% of patients achieved HbA1c <7.0% at 12 weeks.

Conclusion: In this observational study, no treatment-related safety signals using insulin lispro mix 25/75 were detected among Filipino diabetic patients. HbA1c was significantly reduced in Filipino patients with DM at 12 weeks.

Keywords: diabetes mellitus, insulin lispro, Philippines, post-marketing product surveillance

Introduction

Diabetes mellitus (DM) is a major cause of morbidity and mortality worldwide. The prevalence of type 2 DM in the Philippines increased from 5.2% in 2008¹ to 8.2% (4.2 million people) in 2011, and it is expected to affect 7.4 million Filipinos by 2030.² In 2009, it was the eighth leading cause of death in the Philippines, accounting for 22,345 deaths.³

Glycemic control is generally poor among Filipino patients with type 2 DM, and many patients have associated complications and comorbidities. The DiabCare Philippines 2008 survey reported that mean hemoglobin A1c (HbA1c) was 8.03% in Filipinos with type 2 DM, and only 15% of patients achieved the

American Diabetes Association target of HbA1c <7%.^{4,5} In the survey, 78.5% (568/724) of patients were treated with oral anti-diabetic agents and 42% (304/724) were on insulin therapy.⁴ The mean duration of insulin treatment was 4.77 years, with a mean insulin of 41.3 U/day.⁴ Despite evidence of an emerging epidemic of type 2 DM in the Filipino population, improvement in HbA1c remains below the recommended targets. Furthermore, there is a paucity of published data regarding glycemic control among Filipino patients. Safe and effective therapies, therefore, are needed for this population.

Premixed insulin formulations, containing both basal and prandial insulin, are often prescribed because they are superior to long- or intermediate-acting insulin in achieving glycemic control.⁶ Insulin lispro mix 25/75 is a premixed insulin formulation of 25% insulin lispro solution and 75% insulin lispro protamine suspension. Lispro is a rapid-acting insulin analogue with a reduced capacity for self-association and a fast absorption rate that can provide prandial insulin required for meals.⁷ The basal component (insulin lispro protamine suspension) addresses insulin requirements associated with the midday meal and provides basal insulin throughout the day and overnight. This profile gives insulin lispro mix 25/75 the advantages

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of decreasing post-prandial blood glucose excursions, and convenient insulin dosing schedules.

When compared with human insulin 70/30, insulin lispro mix 25/75 significantly decreased post-prandial blood glucose levels and blood glucose excursions among patients with type 2 DM.⁸⁻¹⁰ Hypoglycemia was infrequent in both treatment arms, and no differences in the occurrence of adverse events (AEs) between treatments were found.⁹ Insulin lispro mix 25/75 twice daily was shown to be superior to glyburide 15 mg daily in terms of HbA1c reduction in type 2 DM patients inadequately controlled with glyburide, albeit the mean hypoglycemia rate at endpoint was significantly higher in the insulin lispro mix 25/75 group.¹¹ When compared with once-daily insulin glargine in patients with type 2 DM, the PAIR-IN study showed insulin lispro mix 25/75 twice daily was associated with significantly greater HbA1c reduction.¹² A higher proportion of patients met the treatment goal of HbA1c <7% with insulin lispro mix 25/75 compared with insulin glargine.¹² In that study, insulin lispro mix 25/75 was associated with an increase in overall (but not nocturnal) hypoglycemia.¹² Over a long-term period of 30 months, the DURABLE trial showed that a longer durability of glycemic control was achieved with insulin lispro mix 25/75 compared with insulin glargine in patients with type 2 DM.¹³ No differences were observed in overall, nocturnal or severe hypoglycemia episodes.¹³

This post-marketing surveillance study was conducted to fulfil the regulatory requirement for registration of new drug products granted with monitored release by the Food and Drug Administration of the Philippines. In this study, we investigated the treatment-emergent adverse events (TEAEs) and changes in HbA1c that occurred among Filipino patients with type 1 or type 2 DM treated with insulin lispro mix 25/75 in a real-world setting.

Methodology

Study Design

This was a prospective, non-interventional, post-marketing surveillance study. The regulatory requirement of the Food and Drug Administration of the Philippines for post-marketing surveillance studies is a sample size of 3,000 patients over a period of three years, or 10% of the total marketing projection for the study drug for the three years of monitored release. Based on the latter, this study was designed to enroll at least 400 patients. Patients with type 1 or type 2 DM were followed for 12 weeks over three visits (a baseline visit and two follow-up visits) to determine the proportion of patients who experienced at least one TEAE, the types of serious and non-serious TEAEs, and the change in HbA1c level from baseline to

week 12.

This study was conducted in compliance with the ethical principles stated in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All patients provided written informed consent before starting any study procedure according to Good Clinical Practice.

Patients

Male and female Filipino patients aged 18 years or older with type 1 or type 2 DM based on the World Health Organization criteria for DM were eligible to participate in this study.

Treatment

Patients were treated with insulin lispro mix 25/75 (Humalog® Mix 25™ from Eli Lilly and Company) according to the approved label, as prescribed by the investigator in the routine care of the patient. Treatment pattern and treatment initiation or changes were solely at the discretion of the physician and patient.

Study assessments

The primary outcome measure was the proportion of patients who experienced serious and non-serious TEAEs, as well as the types of TEAEs, as reported by the participating investigators using data collection forms between the start of insulin lispro mix 25/75 therapy following the baseline visit until the final follow-up visit. For each TEAE, the severity level was recorded according to the physician's perceived severity of the event (mild, moderate or severe). The incidence of TEAEs was summarized according to their maximum severity. The cut-off value for hypoglycemia as a TEAE due to insulin lispro mix 25/75 therapy was 3.0 mmol/dL. Severe hypoglycemia was defined as hypoglycemia requiring third party intervention. All TEAEs were classified by the system organ class level and preferred term level of the Medical Dictionary for Regulatory Activities (MedDRA), version 15.1. The secondary outcome measure was the change in HbA1c level from baseline to week 12 visits, as reported by the participating investigators using data collection forms.

Statistical analysis

The safety analysis population consisted of all patients who took at least one dose of insulin lispro mix 25/75 and had at least one post-baseline safety assessment. The analyses of the secondary outcome measures were based on patients who took at least one dose of insulin lispro mix 25/75 and participated in the follow-up visits, and thus had a week 12 (± 3) HbA1c evaluation. Summary tables provide the number of patients with data, the mean and SD for

the continuous variables, the 95% confidence interval (CI) of the mean for the change in HbA1c and the number (%) for the categorical variables.

Subgroups based on factors with a potential impact on disease, including gender, treatment duration, concomitant medicines, body mass index (BMI), disease complications, DM type and history of cardiovascular disease, were identified and used only for data exploratory purposes. Differences between subgroups were determined by t-test for continuous variables with two-group comparisons, one-way analysis of variance for continuous variables with greater than two-group comparisons and Fisher's exact test or chi-square test for categorical variables. The significance level was set at 0.05. The multiplicity was not adjusted. No imputation was applied if data were missing or a patient decided to discontinue from the study. Data were analyzed using SAS software, version 9.1.3.

Results

Patient disposition

Patient disposition is shown in Figure 1. A total of 460 patients were enrolled in the study. One patient was excluded from the safety analysis population due to lack of post-baseline safety assessment. A total of 459 patients were included in the safety analysis population. Of these, 71 patients were excluded from the effectiveness analysis due to absence of their post-baseline HbA1c evaluation between weeks 9 and 15. These patients were not followed up since this was an observational study and there was no intervention. Thus, 388 patients were included in the effectiveness analysis set. Patients were recruited between 2008 and 2012 in 33 centers in the Philippines. The centers included private practices, government clinics, government hospitals and private tertiary hospitals. A total of 59 treating investigators comprising general practitioners, internists, diabetologists and endocrinologists participated in the study.

Baseline characteristics

Table 1 shows the baseline characteristics. Female patients constituted 57.5% of the cohort. There were no significant differences between the genders with respect to age and BMI. More than 70% of patients were aged 30 to 60 years, and 26.1% were older adults (>60 years). Approximately 23% of patients had a normal BMI. The majority of patients (96.9%) had type 2 DM. Most patients were insulin-naïve and only one patient (0.2%) had received prior insulin treatment (data not shown).

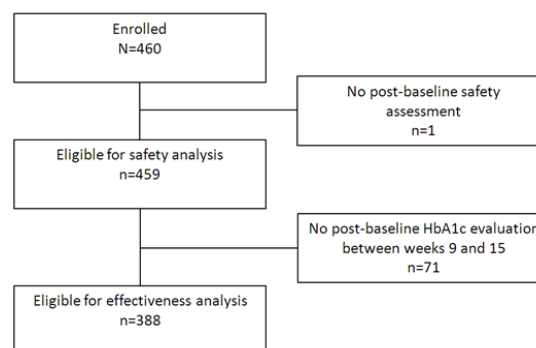


Figure 1: Patient disposition.

HbA1c = hemoglobin A1c; n = number of patients in subgroup; N = total number of patients.

Table 1: Baseline Characteristics by Gender, N=459

	Male (N=195)	Female (N=264)	Total (N=459)
Gender, n (%)			
Male			195 (42.5)
Female			264 (57.5)
Age, years ^a	53.96 (11.1)	53.38 (11.4)	53.63 (11.2)
Age by category, n (%)			
<30 years	3 (1.5)	7 (2.7)	10 (2.2)
30-60 years	140 (71.8)	189 (71.6)	329 (71.7)
>60 years	52 (26.7)	68 (25.8)	120 (26.1)
Weight, kg ^a	68.26 (10.3)	61.93 (10.6)	64.62 (10.9)
BMI, kg/m ^{2a}	25.70 (4.9)	25.13 (4.3)	25.37 (4.6)
BMI by category, n (%)			
Underweight ^b	11 (5.6)	12 (4.5)	23 (5.0)
Normal	36 (18.5)	70 (26.5)	106 (23.1)
At risk	38 (19.5)	61 (23.1)	99 (21.6)
Moderately obese	87 (44.6)	85 (32.2)	172 (37.5)
Severely obese	23 (11.8)	36 (13.6)	59 (12.9)
DM type, n (%)			
Type 1			14 (3.1)
Type 2			445 (96.9)

^aData are presented as mean (SD). ^bBMI categories were as follows: underweight, <18.5 kg/m²; normal, 18.5-22.9 kg/m²; at risk, 23-24.9 kg/m²; moderately obese, 25-29.9 kg/m²; severely obese, ≥30 kg/m². BMI = body mass index; DM = diabetes mellitus. n = number of patients in subgroup; N = total number of patients

A total of 244 patients (53.2%) had pre-existing comorbidities. No significant difference between patients aged ≤65 years and those aged >65 years was detected. For the most commonly reported comorbidities in this study, 159 patients (34.6%) had a history of vascular disorders, 109 patients (23.7%) had metabolism and nutrition disorders and 16 patients (3.5%) had infections and infestations (data not shown).

Treatment-emergent adverse events

The incidence of TEAEs is summarized in Table II. Eighteen patients (3.9%) reported a total of 23 TEAEs, of which 20 were mild and three were moderate. No serious TEAEs or deaths in this study were reported. In addition, no episodes of hypoglycemia were reported. No TEAE was reported for those with a treatment duration less than 11 weeks, age >65 years or those who were underweight. In the following patient subgroups, more than 5% of the patients reported TEAEs: treatment duration 11 to 13 weeks (6.3%), use of any concomitant medication (5.3%) and at risk for obesity (5.1%).

Table II: Incidence of treatment-emergent adverse events, N=459

	Number of patients (%)	Number of events
Any TEAE ^{a,b}	18 (3.9)	23
Severity ^a		
Mild	15 (3.3)	20
Moderate	3 (0.7)	3
Severe	0 (0.0)	
TEAEs possibly related to study drug ^b	0 (0.0)	
Serious TEAEs ^b	0 (0.0)	
TEAEs by treatment duration ^{c,d}		
<11 weeks (n=70)	0 (0.0)	
11-13 weeks (n=219)	14 (6.3)	17
>13 weeks (n=156)	4 (2.6)	6
TEAEs by gender ^d		
Male (n=195)	9 (4.6)	13
Female (n=264)	9 (3.4)	10
TEAEs by concomitant medication ^d		
With concomitant medication (n=301)	16 (5.3)	21
Without concomitant medication (n=158)	2 (1.3)	2
TEAEs by age ^d		
≤65 years (n=398)	18 (4.5)	23
>65 years (n=61)	0 (0.0)	
TEAEs by BMI ^d		
Underweight (n=23) ^e	0 (0.0)	
Normal (n=106)	5 (4.7)	5
At risk (n=99)	5 (5.1)	8
Moderately obese (n=172)	6 (3.5)	7
Severely obese (n=59)	2 (3.4)	3

^aTEAEs occurred after patients were exposed to study drug. As there was no lead-in period in the study, all the adverse events were TEAEs. ^bThe denominator for the percentage calculation was 459. ^cn=445; 14 of 459 patients had missing dose-related information. ^dThe denominator for the percentage calculation was the number of patients in each subgroup. ^eBMI categories were as follows: underweight, <18.5 kg/m²; normal, 18.5-22.9 kg/m²; at risk, 23-24.9 kg/m²; moderately obese, 25-29.9 kg/m²; severely obese, ≥30 kg/m². BMI = body mass index; n = number of patients in subgroup; N = total number of patients; TEAE = treatment-emergent adverse event.

The types of TEAEs are summarized in Table III. The most commonly reported TEAEs were nasopharyngitis (0.9%), urinary tract infection (0.7%), upper respiratory tract infection (0.7%), wound infection (0.4%) and

Table III: Summary of treatment-emergent adverse events, N=459

System Organ Class Preferred term ^a	Number of patients (%)	Number of events	Severity		
			Mild	Mod	Severe
Gastrointestinal disorders^b	3 (0.7)	3			
Abdominal distention	1 (0.2)	1	1	0	0
Abdominal pain upper	1 (0.2)	1	1	0	0
Diarrhea	1 (0.2)	1	1	0	0
Infections and infestations	8 (1.7)	11			
Acute tonsillitis	1 (0.2)	1	1	0	0
Nasopharyngitis	4 (0.9)	4	4	0	0
Urinary tract infection	3 (0.7)	3	2	1	0
Viral pharyngitis	1 (0.2)	1	1	0	0
Wound infection	2 (0.4)	2	1	1	0
Musculoskeletal and connective tissue disorders	1 (0.2)	1			
Myalgia	1 (0.2)	1	0	1	0
Nervous system disorders	2 (0.4)	2			
Headache	2 (0.4)	2	2	0	0
Respiratory, thoracic and mediastinal disorders	4 (0.9)	4			
Cough	1 (0.2)	1	1	0	0
Upper respiratory tract infection	3 (0.7)	3	3	0	0
Skin and subcutaneous tissue disorders	2 (0.4)	2			
Cellulitis	1 (0.2)	1	1	0	0
Rash maculo-papular	1 (0.2)	1	1	0	0
Total	18 (3.9)^c	23	20	3	0

^aTreatment-emergent adverse events were categorized by the system organ class (bold font) and the preferred term level (regular font) of MedDRA, version 15.1. ^bTreatment-emergent adverse events occurred after patients were exposed to study drug. As there was no lead-in period in the study, all the adverse events were treatment-emergent adverse events. ^cSome patients experienced more than 1 adverse event. MedDRA = Medical Dictionary for Regulatory Activities; Mod = moderate; N = total number of patients.

headache (0.4%). One case of urinary tract infection, one case of wound infection and one case of myalgia were reported to be of moderate severity. None of the TEAEs were reported by the investigators to be possibly related to insulin lispro mix 25/75.

Insulin lispro mix 25/75 dosage

Insulin lispro mix 25/75 dosage is summarized in Table IV. Mean (SD) treatment duration was 12.93 (5.7) weeks, and mean average total daily dose was 39.27 (17.3) units or 0.62 (0.29) units/kg. The mean average total daily dose ranged from 0.74 units/kg for underweight (BMI <18.5 kg/m²) patients to 0.49 units/kg for severely obese (BMI ≥30 kg/m²) patients, and was 0.84 units/kg and 0.62 units/kg for patient

Table IV: Summary of Insulin Lispro mix 25/75 dosage, N=459

	Value
Mean total daily dose at baseline, units (SD) ^a	39.44 (17.6)
Mean total daily dose at baseline, units/kg (SD)	0.63 (0.3)
Dose frequency, n (%) ^a	
Once per day	22 (4.8)
Twice per day	435 (94.8)
Three times per day	2 (0.4)
Mean average total daily dose, units (SD) ^b	39.27 (17.3)
Mean average total daily dose, units/kg (SD) ^b	0.62 (0.29)
Mean change from baseline to final total daily dose, units (SD) ^b	0.23 (2.18)
Mean change from baseline to final total daily dose, units/kg (SD) ^b	-0.01 (0.04)
Any dose change, n (%) ^b	
Yes	22 (4.8)
No	423 (92.2)
Reason for dose change, n ^{b, c}	
Lack of effectiveness	26
Adverse event	0
Other	4
Mean treatment duration, weeks (SD) ^b	12.93 (5.7)
Treatment duration by category, n (%) ^b	
<11 weeks	70 (15.3)
11-13 weeks	219 (47.8)
>13 weeks	156 (34.0)
Mean average total daily dose by age, units/kg (SD) ^b	
<30 years (n=10)	0.63 (0.27)
30-60 years (n=317)	0.61 (0.30)
>60 years (n=118)	0.65 (0.29)
Mean average total daily dose by BMI, units/kg (SD) ^b	
Underweight (n=23) ^d	0.74 (0.38)
Normal (n=100)	0.71 (0.31)
At risk (n=98)	0.66 (0.31)
Moderately obese (n=168)	0.57 (0.26)
Severely obese (n=56)	0.49 (0.18)
Mean average total daily dose by diabetes type, units/kg (SD) ^b	
Type 1 (n=7)	0.84 (0.28)
Type 2 (n=438)	0.62 (0.29)

^aThe denominator for the percentage calculations was 459. ^bn=445; 14 of 459 patients had missing dose-related information. ^cSome patients had multiple reasons for dose change. ^dBMI categories were as follows: underweight, <18.5 kg/m²; normal, 18.5-22.9 kg/m²; at risk, 23-24.9 kg/m²; moderately obese, 25-29.9 kg/m²; severely obese, ≥30 kg/m². BMI = body mass index; n = number of patients in subgroup; N = total number of patients.

with type 1 and type 2 DM, respectively. There was no significant difference in the mean average total daily dose among the age categories of <30 years, 30 to 60 years and >60 years. A total of 22 patients (4.8%) had doses titrated, mainly due to a lack of effectiveness. Of these, the dose of 17 patients was titrated once and the dose of five patients

was titrated at least twice. A total of 301 patients (65.6%) received concomitant medications prescribed at the discretion of the site investigators. The most commonly prescribed concomitant medications in this study were indicated for conditions of the cardiovascular system (45.1%). Hypoglycemic agents received included metformin in 85 patients (18.5%) and metformin hydrochloride in 30 patients (6.5%). Fifty-five patients (12%) received simvastatin, 50 patients (10.9%) received amlodipine besylate and 38 patients (8.3%) received telmisartan, all of which were classified as non-hypoglycemic agents.

Effectiveness

Changes in HbA1c across the effectiveness analysis dataset (n=388) are summarized in Table V. Mean (SD) HbA1c for the entire cohort was 9.43% (1.86) at baseline versus 7.40% (1.04) at week 12, with a significant mean (95% CI) change in HbA1c of 2.03% (-2.19, -1.87) over 12 weeks. In all subgroups, HbA1c significantly decreased from baseline to the week 12 visit. Patients on concomitant medications (the majority of which were for conditions of the cardiovascular system) had a significantly greater reduction in HbA1c than patients not on concomitant medications, with a mean HbA1c percentage change of -2.27 versus -1.63, respectively (p=0.0001). Mean HbA1c reduction was 1.12% and 2.06% for patients with type 1 and type 2 DM, respectively. There was no significant difference in the change in HbA1c at 12 weeks between the subgroups for treatment duration, gender, age, BMI or history of cardiovascular disease.

The proportion of patients achieving HbA1c targets is summarized in Table VI. At week 12, the number of patients with HbA1c <7.0% was 141 (36.3%). The percentage of patients with HbA1c <7% ranged from 29.3% for moderately obese (BMI 25-29.9 kg/m²) patients to 57.9% for underweight (BMI <18.5 kg/m²) patients (p=0.049). There was no significant difference in the proportion of patients achieving HbA1c <7% by treatment duration, gender, concomitant medication use or age.

Discussion

In this post-marketing surveillance study among Filipino patients with type 1 or type 2 DM treated with insulin lispro mix 25/75, 3.9% of patients experienced TEAEs, the majority of which were mild. No TEAEs were reported by the investigators to be possibly related to study drug. Mean HbA1c had decreased from a baseline of 9.43% to 7.40% at approximately 12 weeks. The proportion of patients with HbA1c <7% was 36.3% at approximately 12 weeks.

Table V: Effectiveness of Insulin Lispro mix 25/75 by hemoglobin A1c, N=388^a

	Baseline Mean % (SD)	Follow-up visit Mean % (SD)	Change from baseline Mean % (SD)	Change from baseline 95% CI	p-value ^b
HbA1c, entire cohort	9.43 (1.86)	7.40 (1.04)	-2.03 (1.59)	-2.19, -1.87	
HbA1c by treatment duration					
<11 weeks (n=38)	9.79 (2.56)	7.38 (1.06)	-2.41 (2.33)	-3.18, -1.65	0.99
11-13 weeks (n=219)	9.32 (1.77)	7.37 (0.94)	-1.96 (1.48)	-2.15, -1.76	
>13 weeks (n=122)	9.47 (1.73)	7.41 (1.15)	-2.06 (1.50)	-2.33, -1.79	
Missing (n=9)	9.92 (2.14)	8.13 (1.33)	-1.79 (1.35)	-2.67, -0.91	
HbA1c by gender					
Male (n=164)	9.38 (1.77)	7.35 (0.96)	-2.03 (1.58)	-2.27, -1.78	0.86
Female (n=224)	9.46 (1.93)	7.44 (1.09)	-2.03 (1.59)	-2.24, -1.82	
HbA1c by concomitant medication					
With concomitant medication (n=243)	9.67 (1.91)	7.41 (1.00)	-2.27 (1.73)	-2.49, -2.05	0.0001
Without concomitant medication (n=145)	9.02 (1.69)	7.39 (1.10)	-1.63 (1.22)	-1.83, -1.43	
HbA1c by age					
≤65 years (n=343)	9.44 (1.85)	7.41 (1.05)	-2.04 (1.58)	-2.21, -1.87	0.92
>65 years (n=45)	9.31 (1.94)	7.35 (0.97)	-1.96 (1.65)	-2.45, -1.46	
HbA1c by BMI					
Underweight (n=19) ^c	8.72 (2.26)	7.05 (0.82)	-1.67 (1.94)	-2.61, -0.74	0.99
Normal (n=87)	9.42 (2.03)	7.41 (1.24)	-2.03 (1.68)	-2.39, -1.66	
At risk (n=84)	9.28 (1.61)	7.31 (0.95)	-1.98 (1.28)	-2.25, -1.70	
Moderately obese (n=147)	9.60 (1.89)	7.45 (0.96)	-2.15 (1.72)	-2.43, -1.87	
Severely obese (n=51)	9.46 (1.66)	7.54 (1.06)	-1.91 (1.31)	-2.28, -1.54	
HbA1c by DM type					
Type 1 (n=11)	9.39 (1.93)	8.27 (1.90)	-1.12 (0.74)	-1.62, -0.62	0.023 ^d
Type 2 (n=377)	9.43 (1.86)	7.38 (0.99)	-2.06 (1.60)	-2.22, -1.89	
HbA1c by cardiovascular disease					
With cardiovascular disease (n=90)	9.48 (1.81)	7.25 (1.00)	-2.23 (1.78)	-2.61, -1.85	0.70
Without cardiovascular disease (n=298)	9.45 (1.88)	7.48 (1.09)	-1.97 (1.48)	-2.14, -1.81	

^aBased on the effectiveness analysis dataset, n=388. ^bP-value was used for detecting the difference of the mean change in HbA1c from the baseline to the final visit across the subgroups.

^cBMI categories were as follows: underweight, <18.5 kg/m²; normal, 18.5-22.9 kg/m²; at risk, 23-24.9 kg/m²; moderately obese, 25-29.9 kg/m²; severely obese, ≥30 kg/m². ^dDue to the small population of patients with type 1 DM, no conclusions may be drawn from the difference in comparison to type 2 DM patients. BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; HbA1c = hemoglobin A1c; n = number of patients in subgroup; N = total number of patients.

The proportion of Filipino patients who experienced TEAEs in this study was less than that in previous studies. For instance, during the 24-week initiation phase of the DURABLE trial, 6.2% of patients in the insulin lispro mix 25/75 group experienced at least one serious AE.¹⁴ In the PAIR-IN study of insulin lispro mix 25/75, which was conducted over 16 weeks, 3.8% of patients experienced TEAEs that required hospitalisation.¹² The types of TEAEs reported were generally similar to those observed in previous studies, and none of the TEAEs were considered related to treatment with insulin lispro mix 25/75, which is consistent with the previous study of combined therapy with insulin lispro mix 25/75 plus metformin versus insulin glargine plus metformin.¹²

Hypoglycemia is a potentially serious AE associated with therapies for glycemic control. In previous studies,^{10,11} the mean hypoglycemia rates associated with insulin lispro mix 25/75 ranged from 0.05 to

0.30 episodes per patient per 30 days. In this study, however, no hypoglycemic episodes were reported. The mean average total daily dose indicates that the patients in this study were not underdosed. Whilst this finding differs from that of previous studies of insulin lispro mix 25/75, it is consistent with a recent study conducted in Filipino type 2 DM patients on combination insulin therapy, in which no episodes of hypoglycemia were noted.¹⁵ The authors of that study concluded that the lack of hypoglycemic episodes might be attributable to patient compliance with automatic snacking. It is customary for Filipinos to snack between meals on high-carbohydrate foods such as rice cakes, traditional pastries, bread or noodles. This may have minimized glucose excursions, as Filipino patients may not have experienced hypoglycemic symptoms that would make them miss insulin injections and/or adjust their regimen

haphazardly.¹⁵ It is therefore possible that the lack of hypoglycemic episodes observed in this study was due to snacking practices in the Philippines. Alternatively, patients may have been reluctant to report minor hypoglycemic episodes, or may not have been aware of hypoglycemic symptoms.

Table VI: Proportion of patients achieving hemoglobin A1c targets, N=388^a

	Number of patients (%)	p-value ^b
HbA1c <7.0%, entire cohort		
At baseline	10 (2.6)	
At follow-up visit 2 (12±three weeks)	141 (36.3)	
HbA1c <7% by treatment duration ^c		0.29
<11 weeks (n=38)	19 (50.0)	
11-13 weeks (n=219)	74 (33.8)	
>13 weeks (n=122)	45 (36.9)	
Missing (n=9)	3 (33.3)	
HbA1c <7% by gender ^c		0.92
Male (n=164)	59 (36.0)	
Female (n=224)	82 (36.6)	
HbA1c <7% by concomitant medication ^c		0.83
With concomitant medication (n=243)	87 (35.8)	
Without concomitant medication (n=145)	54 (37.2)	
HbA1c <7% by age ^c		1.00
≤65 years (n=343)	125 (36.4)	
>65 years (n=45)	16 (35.6)	
HbA1c <7% by BMI ^{c,d}		0.049
Underweight (n=19)	11 (57.9)	
Normal (n=87)	36 (41.4)	
At risk (n=84)	35 (41.7)	
Moderately obese (n=147)	43 (29.3)	
Severely obese (n=51)	16 (31.4)	
HbA1c <7% by DM type ^e		0.75 ^a
Type 1 (n=11)	3 (27.3)	
Type 2 (n=377)	138 (36.6)	

^aBased on the effectiveness analysis dataset, n=388. ^bP-value was used for detecting the association between the subgroups and HbA1c target achievement. ^cThe denominator of percentage calculation is the number of patients in each subgroup. ^dBMI categories were as follows: underweight, <18.5 kg/m²; normal, 18.5-22.9 kg/m²; at risk, 23-24.9 kg/m²; moderately obese, 25-29.9 kg/m²; severely obese, ≥30 kg/m². ^eDue to the small population of patients with type 1 DM, no conclusions may be drawn from the difference in comparison to type 2 DM patients. BMI = body mass index; DM = diabetes mellitus; HbA1c = hemoglobin A1c; n = number of patients in subgroup; N = total number of patients;

A relatively small proportion of patients (4.8%) changed dose during the study period, and most dose changes were due to lack of effectiveness. This may be because physicians and/or patients were cautious to change treatment within the relatively short study duration. Alternatively, there may have been little need to adjust doses to optimize glycemic control since there were no cases reported of hypoglycemia.

In this study, HbA1c level was significantly

reduced from baseline to follow-up visit. The mean HbA1c reduction was -2.03%, which is greater than that reported in the 24-week initiation phase of the DURABLE trial (-1.8%)¹⁴ and the 16-week treatment phase of the PAIR-IN trial (-1.3%).¹² This difference may be attributable to the lower baseline HbA1c levels in the insulin lispro mix 25/75 arms of the previous studies, which were 9.1% in DURABLE¹⁴ and 8.7% in the 16-week treatment arm of PAIR-IN,¹² versus 9.43% in this study. Patients on concomitant medications had a significantly greater reduction in HbA1c than patients not on concomitant medications, which may have been because patients on concomitant medication had higher baseline HbA1c (9.67% versus 9.02%).

The proportion of patients who achieved HbA1c <7.0% in this study was 36.3% at approximately 12 weeks, which is less than that reported in the 24-week initiation phase of the DURABLE trial (47.5%)¹⁴ and the 16-week treatment phase of the PAIR-IN trial (42%).¹² These differences may be due to the shorter duration of this study (as a study analysis population with a longer follow-up period is likely to have a greater number of patients with HbA1c <7%), and/or because a relatively small proportion of patients changed dose during the study period. The proportion of obese patients who achieved HbA1c <7% was relatively low, which may be explained by the observation that moderately and severely obese patients received a lower dose of insulin lispro mix 25/75 compared to patients in other BMI categories. Due to the small population of patients with type 1 DM, no conclusion can be drawn from the difference in HbA1c reduction in comparison to type 2 DM patients.

While this post-marketing surveillance study has the advantage of collecting data in a real-world setting, it is associated with several inherent limitations. For instance, the study design was observational with no control group, and therefore the safety profile of insulin lispro mix 25/75 could not be compared to that of other insulins. The short observational period did not allow assessment of long-term TEAEs, and, according to regulatory requirements, a population of only 10% of the total marketing projection for the study drug for the three years of monitored release was enrolled in the study. Use of concomitant medications was not controlled. Also, no data on weight change or duration of DM since diagnosis were gathered. Nonetheless, this is the first study to investigate the TEAEs that occur among Filipino patients with DM treated with insulin lispro mix 25/75 in a real-world setting. This study provides data on the mean daily dose of insulin lispro mix 25/75 in Filipino patients and the resultant TEAEs across a broad spectrum of DM patients, including older adults (age >60 years),

who formed more than a quarter of the cohort. The results provide further information to physicians caring for Filipino patients with type 1 and type 2 DM.

Conclusion

No treatment-related safety signals with insulin lispro mix 25/75 among Filipino patients were detected in this observational study, irrespective of gender, age, BMI, concomitant medications or type of DM. The HbA1c reduction was significant and HbA1c targets were achieved at approximately 12 weeks in a proportion of Filipino patients with type 1 and type 2 DM using insulin lispro mix 25/75.

Acknowledgements

We thank the patients, their families, the study sites, and the study personnel who participated in this study. This study was sponsored by Eli Lilly and Company. Medical writing support was provided by Andrew Sakko from inVentiv Health Clinical and editorial support was provided by Noelle Gasco from inVentiv Health Clinical, funded by Eli Lilly and Company.

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